selecting one or more FK506 analogs of interest that does not bind FKBP-12, wherein the FK506 analog has a K_d for FKBP-12of at least 10 μM; and

assaying of one or more of the analogs of interest for activity in promoting nerve cell growth.

REMARKS

Claims 8, 12 and 14 are canceled herein. Claim 6 is amended to incorporate the limitations of claims 8 and 14. Claims 7, 9, 10, 11 and 20 are amended to correct grammar, form, or dependency.

No new matter is added. Reconsideration of the subject application is respectfully requested.

Continued Prosecution and Restriction Requirement

Applicant thanks the Examiner for the acknowledgement of the Continued Prosecution Application. Applicant further acknowledges that the restriction requirement has been made final, and that claim 19 is withdrawn from consideration.

Drawings

Applicant acknowledges that the drawings have not been reviewed. Applicant defers any further amendments to the drawings until a formal review of the drawings is received.

Specification

The Office action requested amendment of the title of the specification. Applicant has amended the title to be "METHODS FOR SCREENING AGENTS THAT STIMULATE NERVE CELL GROWTH," thereby removing the rejection.

The Office action notes that page 17, line 23 refers to U.S. Patent No. 5,654,332, but the Examiner was unable to obtain or locate this patent. A copy of U.S. Patent No. 5,654,332 is enclosed for the Examiner's convenience as Exhibit A.

The Office action requested clarification of the direction in the amendment filed on February 20, 2001. This amendment indicated a directed insertion to page 1, line 14, before

"(4)." Applicant apologizes for the typographical error. Applicant requests that this insertion should be made on page 11, as indicated in the present amendment, and not on page 1.

Claim Objections

Claims 7-11, 14, and 16-18 are objected to as being in improper dependent form. Applicant respectfully disagrees with this objection. However, solely in the interest of advancing prosecution, and not for reasons of patentablility, the claims have been amended, rendering the objection moot.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 11-12 are rejected as allegedly being indefinite in the use of the terms "significantly inhibit" and "low," when referring to the inhibition of rotamase activity. Applicant respectfully disagrees with this rejection.

One of skill in the art can readily assess a significant inhibition of rotamase activity using statistical methods well known in the art. For example, Liu and Walsh (*Proc. Natl. Acad. Sci. USA* 87:4028-4032, 1990, submitted herewith as Exhibit B) disclose that *E. coli* rotamase is not inhibited by Cyclosporin A. This references clearly sets forth parameters for determining if rotamase is inhibited, and what constitutes significant inhibition (see page 4030, column 2, sections entitled "*Comparison of rotamase activities...*" and "*Inhibition with CsA*"). Thus, Applicant submits that significant inhibition of rotamase activity is clear and definite to one of skill in the art. Reconsideration and withdrawal of the rejection is respectively requested.

Claims 8-10, 14, and 16-17 are rejected as allegedly being indefinite in reciting non-binding FKBP-12 analogs that bind FKBP-12 at a certain affinity. Claims 8 and 14 are canceled herein. Applicant respectfully disagrees with the rejection as applied to claims 9-10 and 16-17, as non-binding FKBP-12 analogs are clearly defined in the specification by their binding constants for FKBP-12. However, solely in the interest of advancing the prosecution of the application, the claims have been amended, rendering the rejection moot.

Claims 7, 11, and 18 were rejected as allegedly the method steps did not specify selecting for rotamase activity, thereby rendering the claims indefinite. Claim 18 has been canceled. Applicant respectfully disagrees with the rejection as applied to claims 7 and 11. The ability of a compound is an inherent property of the FK506 analog that binds FKBP-12 with an apparent K_d

of greater than 10 μM. In order to practice the claimed method, an independent assessment of the inhibition of rotamase activity need not be done at the time of screening. Thus, the claimed methods correctly do not recite the step of assessing rotamase activity. However, solely to advance prosecution of the subject application, claims 7 and 11 have been amended to recite that the FK506 analog does not inhibit rotamase activity.

Claim 20 was rejected as being indefinite for depending on a canceled claim. Claim 20 has been amended to correct dependency, thereby removing the rejection.

Rejections Under 35 U.S.C. §102

Claims 6-12, 12-18 and 20-21 were rejected as allegedly being anticipated by Steiner et al. (U.S. Patent No. 5,801,197, hereinafter the '197 patent). Applicant respectfully disagrees with this rejection.

The '197 patent teaches selecting compounds that bind FKBP-12, evaluating these compounds with a high affinity for FKBP12 for their effect on neurite outgrowth. For example, the '197 patent states "The novel neurotrophic FKBP inhibitor compounds of this invention have an affinity for the FK506 binding proteins such as FKBP-12. When the neurotrophic compounds of the invention are bound to FKBP, they have been found to inhibit the prolyl-peptidyl cis-trans isomerase activity, or rotamase activity of the binding protein and unexpectedly stimulate neurite growth." The binding of the compounds to FKBP-12 is described and documented in the '197 patent. However, the '197 patent specifically teaches the selection of a compound that binds FKBP-12 with a high affinity. The '197 patent does not teach, nor render obvious, the selection of an FK506 analog that does not bind FKBP12.

The Examiner appears to contend that in selecting FK506 analogs that bind FKBP-12 with high affinity, and then screening FK506 analogs that bind FKBP-12 for their ability to promote neurite outgrowth, compounds that do not bind FKBP-12 are inherently selected. Applicant respectfully disagrees. Even if FK506 analogs that do not bind FKBP-12 are inherently separated in the process of evaluating FKBP-12 binding, the '197 patent does not teach specifically evaluating these non-binders for their ability to promote neurite outgrowth. By specifically teaching selection of FK506 analogs that bind FKBP-12, the '197 patent *teaches away* from selecting FK506 analogs that do not bind FKBP-12, and from testing these compounds for any effect, let alone their ability to promote neurite outgrowth. Thus, the '197

patent does not anticipate, nor render obvious, claims 6-12, 14-18, and 20-21. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 6-12, 14-18 and 20-21 were rejected as allegedly being anticipated by Amistead et al. (U. S. Patent No. 5,717,092).

Amistead et al. teaches selecting compounds that bind FKBP-12, evaluating these compound with a high affinity for FKBP12 for their effect on neurite outgrowth. Specifically, Amistead et al. states (column 15, lines 26-29) "The compounds of this invention are characterized by their ability to stimulate neurite growth through their binding affinity to FKBP12." And (column 15, lines 48-51) "The neurotrophic activity of the compounds of this invention is directly related to their affinity for FKBP12 and their ability to inhibit FKBP12 rotamase activity." Amistead et al. teaches (see examples 10-11) selecting a compound that binds FKBP-12 *with high affinity* and screening for the ability of the compound to promote neurite outgrowth. Thus, Amistead et al. *teaches away* from the claimed methods, which include selecting an FK506 analog that does not bind FKBP-12.

Thus, Applicant submits that Amistead et al. does not anticipate claims 6-12, 14-18 and 20-21. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 6-12, 24-18 and 20-21 were rejected as allegedly being anticipated by Steiner et al. (*Nature Medicine* 3:421-8, 1997).

Steiner et al. teaches evaluation of FK506 analogs for FKBP12 binding activity. However, Steiner et al. teaches that compounds that bind FKBP12 with a high affinity promote neurite outgrowth, and suggest selecting FK506 analogs based on this activity. Steiner et al. does not suggest selecting FK506 analogs that do not bind FK506. By teaching that the characteristic of FKBP12 binding is desirable, Steiner et al. *teaches away* from the claimed methods (which include selecting an FK506 analog that **does not** bind FKBP12).

Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

If any minor matters remain to be addressed, the Examiner is respectfully requested to call the undersigned patent attorney at the telephone number listed below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 
William D. Noonan, M.D.
Registration No. 30,878

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 226-7391
Facsimile: (503) 228-9446

Marked-up Version of Amended Claims and Specification
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

In the Specification:

Please see attached pages 1, 11a-11b, and 34.

In the claims:

6. (Thrice Amended) A method of identifying a non-binding FK506 analog that stimulates nerve cell growth, the method comprising:

screening a plurality of FK506 analogs for binding to FKBP-12[,];

selecting a FK506 analog that does not bind FKBP-12 wherein the compound that does not bind FKBP-12 is a compound that has an apparent K_d for FKBP-12 of greater than 10 μM; and

assaying the FK506 analog that does not bind FKBP-12 for activity in promoting nerve cell growth, thereby identifying a non-binding FK506 analog that stimulates nerve cell growth.

claim 1 to previous 112 2nd ¶

7. (Amended) The method of claim 6, wherein the [agent is selected irrespective of] the method does not comprise selecting an agent based on its ability to inhibit FKBP-12 rotamase activity.

Please cancel claim 8.

9. (Amended) The method of claim 6, wherein [selecting a] the FK506 analog [that does not bind FKBP-12 comprises selecting a FK506 analog that binds to FKBP-12 with] has an apparent K_d for FKBP-12 of greater than 30 μM.

10. (Amended) The method of claim 6, wherein [selecting a] the FK506 analog [that does not bind FKBP-12 comprises selecting a FK506 analog that binds to FKBP-12 with] has an apparent K_d for FKBP-12 of greater than 100 μM.

11. (Amended) The method of claim 6 wherein [selecting a] the FK506 analog [that does not bind FKBP-12 comprises selecting a FK506 analog that] does not [substantially] inhibit FKBP-12 rotomase activity.

Please cancel claims 12 ,14 and 18.

20. (Amended) A method of identifying a FK506 analog that stimulates nerve cell growth, the method comprising:

screening FK506 analogs, selected from group consisting of the analogs of claim [13]21, for binding to FKBP-12;

selecting one or more FK506 analogs of interest that does not bind FKBP-12, wherein the FK506 analog has [with] a K_d for FKBP-12 of at least 10 μM; and

[performing additional] assaying of one or more of the analogs of interest for activity in promoting nerve cell growth.